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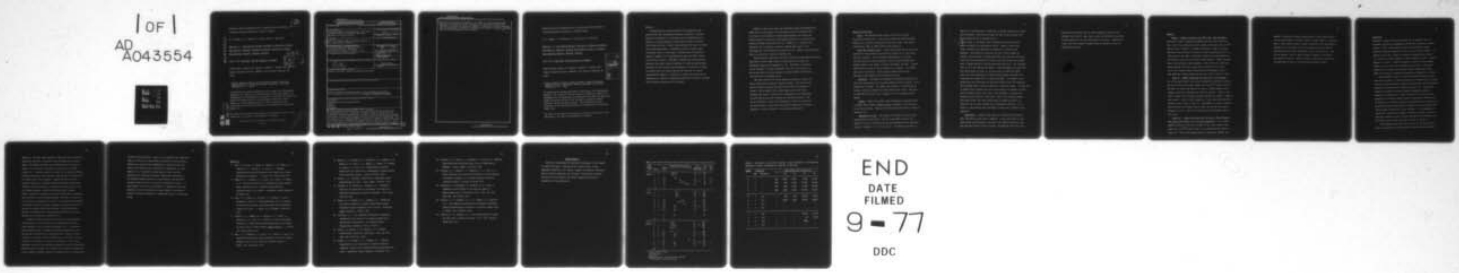

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Venezuelan Equine Encephalomyelitis: Protective and Toxic Effects of a Nuclease-Resistant Derivative of Poly(I)·Poly(C)

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Short Title: Poly(ICLC) and VEE Infection In Monkeys

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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Abstract

Polyriboinosinic·polyribocytidylic acid stabilized with poly-l-lysine and carboxymethylcellulose, poly(ICLC), favorably alters the pathogenesis of Venezuelan equine encephalomyelitis infection in rhesus monkeys by decreasing the number of monkeys that become detectably viremic and by delaying the onset of viremia in the remaining monkeys. Poly(ICLC) is known to induce high, circulating levels of interferon in primates and the interferon system is assumed to be the mechanism by which poly(ICLC) exerts its antiviral activity. Poly(ICLC) treatment was associated with mortality only under certain conditions of infection and handling. The death of some infected-treated monkeys in the absence of death in monkeys that were either infected and untreated or treated and uninfected suggests a synergistic toxicity resulting from the combination of infection, handling and poly(ICLC) treatment, although other possible explanations are discussed.

Studies in vitro have shown that Venezuelan equine encephalomyelitis (VEE) virus is susceptible to the antiviral effect of interferon (IF) [7, 8] and in vivo studies in Syrian golden hamsters have shown that poly(I)·poly(C) is effective in increasing resistance to infection with virulent Trinidad strain VEE virus [8]. Kuehne et al. reported that poly(ICLC) was an effective antiviral compound when given to mice challenged with the Trinidad strain VEE virus [9]. However, poly(I)·poly(C) is not an effective IF inducer in monkeys (3).

Poly(I)·poly(C) stabilized with poly-l-lysine and carboxymethylcellulose [poly(ICLC)] induces high levels of circulating IF in rhesus and cynomolgus monkeys and chimpanzees [1, 2]. Poly(ICLC) is effective in the treatment of simian hemorrhagic fever [3], yellow fever [4], and street rabies [5] virus diseases in rhesus monkeys and hepatitis virus infection in chimpanzees [6].

VEE virus infection of rhesus monkeys is generally benign [10], with a characteristic biphasic febrile response. The initial fever and mild anorexia roughly coincides with the onset and duration of viremia. The secondary fever usually begins on the fifth day. Uncomplicated cases of infection are accompanied by the development of serum neutralizing (SN) antibody and uneventful recovery. The use of poly(ICLC) to alter the pathogenesis of VEE virus infection in rhesus monkeys is described with evidence suggestive of possible synergistic toxicity between VEE infection and poly(ICLC).

Materials and Methods

Virus. The Trinidad donkey strain of VEE virus has been described previously [9]. Inocula were diluted with modified Hank's balanced salt solution containing 2% fetal calf serum. The inocula contained 50, 1000, or 1800 pfu/ml and were given sc.

Virus and antibody assays. Serial 10-fold dilutions of sera were assayed for virus content by the method of Earley et al. [11] using Vero cell cultures. For SN antibody determinations, an initial 10-fold dilution of serum followed by serial 2-fold dilutions were assayed using a virus inocula of 100 to 200 plaques per well. Crystal violet stain was used to aid in enumeration of plaques. All assays were done in triplicate. Eighty percent plaque reduction was selected as the endpoint for neutralization titers.

Poly(ICLC). Poly(ICLC) was prepared as previously described [1]. The final concentration of the parent compound, poly(I)·poly(C), in the complex was 2.0 mg/ml. The complex was stored at 4 C and diluted in an equal volume of pyrogen-free 0.85% saline prior to use. Each dose of poly(ICLC) was given iv at a dosage of 0.3 or 3.0 mg/kg of body weight.

Animals. Thirty-six healthy, well-conditioned, young adult male or female rhesus monkeys (Macaca mulatta) weighing 3-4 kg were used in the three studies. Monkeys were housed and maintained as previously described [2].

Experimental design. The regimen of treatment with poly (ICLC) was identical in each study. The first poly(ICLC) injection was given 8 hr prior to virus inoculation with subsequent daily injections on days 1 through 4, 7, 9, 11, 15 and 17. All monkeys were bled on

days 0 to 17 postinfection at 1600 hours to detect viremia and to assay for SN antibody. They were bled again on days 32 and 42 (Study III) for determination of SN antibody titers.

In Study I, the monkeys were restrained in primate restraint chairs throughout the experimental period. Femoral arterial and venous catheters were implanted in 8 monkeys for injection and sampling. Each monkey was allocated into one of three groups as follows: two were given 3.0 mg/kg poly(ICLC) only, two were inoculated with virus and sham-treated with saline, and four monkeys were treated with 3.0 mg/kg poly(ICLC) and inoculated with VEE virus. The challenge dose of virus was 1000 pfu per monkey. Fourteen monkeys were allocated into three groups in Study II: two were given 3.0 mg/kg poly(ICLC) only, four were challenged with VEE and sham-treated, and eight were challenged and treated with 3.0 mg/kg poly(ICLC). All monkeys in the second study were maintained in cages and catheters were not implanted. The challenge dose of virus was reduced to 50 pfu per monkey. In Study III, 14 monkeys were allocated into one of four groups: two monkeys received drug (3.0 mg/kg) alone, while each of the remaining 12 monkeys were inoculated with 1800 pfu of VEE virus. Four of the infected monkeys were sham-treated, four were treated with 0.3 mg/kg poly(ICLC) per injection and four were treated with 3.0 mg/kg per injection. As in Study II, these monkeys were maintained in cages and no catheters were implanted.

Calculation. Geometric mean values for viremia and SN antibody were calculated at each time of sampling. In the calculation of mean peak viremia and SN antibody, one-half of the lowest detectable value was used when negative values occurred. The minimum serum virus titer

detected was 100 pfu/ml and the lowest detectable reciprocal SN antibody titer was 10. Mean time to death was calculated based only on dead monkeys and was thus unaffected by survivors. Antibody and virus titers were compared between groups by Student's t-test on log-transformed data.

Results

Study I. Monkeys challenged with VEE virus, 1000 pfu/monkey. VEE virus infected, sham-treated monkeys had detectable viremia on day 1 after virus inoculation which reached a mean peak titer of $10^{4.3}$ pfu/ml on day 2 (Table 1). Monkeys C-F (Table 1, Study 1) treated initially with poly(ICLC) 8 hr prior to virus inoculation had a 2- to 7-day delay in the onset of detectable viremia, but peak viremia was not different from that of the sham-treated monkeys. Deaths occurred only in the infected, treated monkeys. Three of the four infected, treated monkeys died with a mean time to death of of 14.3 days. Two of four treated monkeys had detectable SN antibody by day 14 (one additional treated monkey died on day 12 with a titer of 1:40).

Study II. Monkeys challenged with VEE virus, 50 pfu/monkey. All of the sham-treated virus control monkeys were detectably viremic on day 4, when the mean peak viremia titer was $10^{2.6}$ pfu/ml (Table 1). The onset of viremia was delayed 3-5 days in treated monkeys; peak viremia titers were unchanged from infected controls. However, only three of eight virus inoculated-treated monkeys (E-G, Table 1, Study II) were viremic. Three of eight (monkeys E, F and H) had detectable SN antibody titers (Table 1, Study II). One monkey (G, Table 1, Study II) with detectable circulating virus on day 4 did not have detectable antibody by day 14. None of the poly(ICLC)-treated monkeys died in this study.

Study III. Monkeys challenged with VEE virus, 1800 pfu/monkey, and treated with either 0.3 or 3.0 mg/kg poly(ICLC). As in Study I, monkeys given virus alone were viremic on day 1 and reached a mean peak titer of $10^{3.8}$ pfu/ml on days 2 or 3 postinoculation (Table 1, Study III). Two of four monkeys given 0.3 mg/kg were viremic; one

(monkey E) exhibited a bimodal response with a late viremia on day 7 and the other (monkey F) showed a delay of 3 days (Table 1, Study III). Both of these monkeys given 0.3 mg/kg of poly(ICLC) had detectable SN antibody by day 10 whereas none of the monkeys given 3.0 mg/kg of poly(ICLC) had detectable SN antibody by this time (Table 2). Two of four monkeys (I and J, Table 2) given 3.0 mg/kg of poly(ICLC) had antibody by day 32. Monkey K (Table 1, Study III) treated with 3.0 mg/kg died on day 15, but was never detectably viremic.

Discussion

Poly(ICLC) through interferon induction has an important role in favorably altering the pathogenesis of VEE virus infection of rhesus monkeys. Fewer treated monkeys (10/20) were detectably viremic following challenge compared with all ten virus control monkeys. In addition, mean time to onset of viremia was significantly delayed ($P < 0.001$) in treated monkeys (6.2 days) compared to that of control monkeys (2.2 days). Viremia developed in seven of the ten treated monkeys on day 5 and 6 when poly(ICLC) was not given. Additional studies will be required to determine whether continuous therapy might have delayed or completely prevented the appearance of viremia.

Treated monkeys (Table 2) develop detectable SN antibody later than control monkeys, a finding consistent with observations in yellow fever virus-infected monkeys treated with poly(ICLC) which had delayed appearance of antibody when viremia was delayed [4]. The delayed viremia and consequent delayed antigenic stimulation permits a simplistic interpretation of cause and effect for the the delayed appearance of antibody; however, there are many other variables that are difficult to evaluate including the observation that poly(ICLC) is an effective adjuvant when given in combination with inactivated VEE [13] and swine influenza [14] virus vaccines. It is reasonable to assume that treated viremic monkey G in Study II (Table 1) with no detectable antibody by day 14 merely developed later antibody as did the monkeys given similar treatment in Study III (Table 2).

Of the monkeys that died, three of four (C, D, and E, Study 1) were in the group that was restrained in chairs and had catheters

implanted. The other death (monkey K, Study III) also occurred in a group which received a relatively large challenge dose of virus. None of the monkeys died when the challenge dose of virus was low (Study II) or the dose of poly(ICLC) was reduced to 0.3 mg/kg (Study III). A relevant question is posed, as to whether poly(ICLC) treatment potentiated this infection since VEE virus infection does not normally kill rhesus monkeys. Neither VEE virus infected, untreated monkeys nor poly(ICLC)-treated uninfected monkeys died. Therefore one may assume that a synergistic toxicity results from the combined exposure to VEE virus and poly(ICLC) treatment. However, poly(ICLC) treatment may not have specifically potentiated this infection for the following reasons. VEE virus is sensitive to the effects of interferon in vitro [7, 8]; fewer infected monkeys are viremic following poly(ICLC) treatment and treated monkeys did not have increased viremias when compared to untreated monkeys. Further, no potentiation of infection was observed in VEE virus infected mice treated with poly(ICLC) [12].

Studies by others indicate that the toxicity of unstabilized poly(I)·poly(C) increases when given in combination with other toxic substances such as adenine arabinoside [15]. It therefore seems reasonable that 3.0 mg/kg of poly(ICLC) represents close to the maximum tolerated dose in unstressed rhesus monkeys and that toxicity is increased by other stresses; (e.g., infection, the use of chairs for restraint, or the use of catheters). The specific mechanism involved in this possible synergism has not been determined. Reduced vascular clearance of poly(ICLC) with resultant accumulation of the compound following repetitive treatments may be involved and is

currently being evaluated. Gleiser et. al described the lympholytic effect of VEE virus in lymph nodes and spleens of infected rhesus monkeys and leukopenia with lymphopenia in infected burros [16]. Kastello and Spertzel later confirmed this lymphopenia in rhesus monkeys [17]. Poly(ICLC) has been shown to cause transient leukopenia and lymphopenia (authors' unpublished observations). The combined lymphocytotoxicity of VEE infection and poly(ICLC) treatment might also play a role in the synergistic toxicity. It would appear that the use of poly(ICLC) in combination with other compounds which have potential for being harmful to the patient should be evaluated thoroughly in animal models prior to evaluation in man.

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Table 1. Effect of poly(ICLC) treatment on viremia of individual monkeys challenged with Trinidad strain VEE virus.

Study (Challenge dose)	Monkey	VEE	Poly(ICLC) (mg/kg)	Viremia by day after inoculation 0 1 2 3 4 5 6 7 8 9 10 11 12	Titer (log_{10} PFU/ml) Peak	Titer (log_{10} PFU/ml) Mean	SNAb titer day 14	Time to death (days)
I	A	+	-	+ + + + +	4.6	4.3	320	
(1000 PFU)	B	+	-	+ + + + +	4.0		320	
	C	+	3.0	+ + + +	3.4		40	12
	D	+	3.0	+ + + +	4.8	4.2	40	20
	E	+	3.0	+ + + + + + +	4.6		ND†	11
	F	+	3.0	+ + + + + + +	3.9		80	
	G, H	-	3.0					
II	A	+	-	+ + + +	3.0		320	
(50 PFU)	B	+	-	+ + + + +	2.6	2.6	640	
	C	+	-	+ + + + +	2.0		1280	
	D	+	-	+ + + + +	2.9		640	
	E	+	3.0	+ + + + +	4.5		2560	
	F	+	3.0	+ + + + + + +	4.0		640	
	G	+	3.0	+ + + + + + +	2.3		ND	
	H	+	3.0	+ + + + + + +	1.7‡	2.4	320	
	I	+	3.0	+ + + + + + +	1.7		ND	
	J	+	3.0	+ + + + + + +	1.7		ND	
	K	+	3.0	+ + + + + + +	1.7		ND	
	L	+	3.0	+ + + + + + +	1.7		ND	
	M, N	-	3.0					
III	A	+	-	+ + + + +	4.4		2560	
(1800 PFU)	B	+	-	+ + + + +	3.7	3.8	5120	
	C	+	-	+ + + + +	4.1		5120	
	D	+	-	+ + + + +	3.0		5120	
	E	+	0.3	+ + + + + + +	3.8		320	
	F	+	0.3	+ + + + + + +	3.7	2.7	1280	
	G	+	0.3	+ + + + + + +	1.7		ND	
	H	+	0.3	+ + + + + + +	1.7		ND	
	I	+	3.0	+ + + + + + +	2.1		ND	
	J	+	3.0	+ + + + + + +	1.7	1.8§	ND	
	K	+	3.0	+ + + + + + +	1.7		ND	15
	L	+	3.0	+ + + + + + +	1.7		ND	
	M, N	-	3.0					

+ = Days of poly(ICLC) treatment.

* Day of peak viremia.

† Not detected.

‡ Assigned value, one-half of minimum detectable viremia level.

§ $P < 0.001$ compared to untreated control group.

Table 2. The effect of poly(ICLC) treatment on the development of neutralizing antibody in monkeys challenged with 1800 pfu of VEE virus.

MONKEY	TREATMENT		DAYS AFTER VIRUS INOCULATION				
	VEE	POLY(ICLC)	7	10	14	32	42
A	+	-	640	1,280	2,560	2,560	10,240
B	+	-	640	640	5,120	10,240	10,240
C	+	-	320	640	5,120	5,120	20,480
D	+	-	640	2,560	5,120	10,240	10,240
E	+	0.3	-	320	320	10,240	5,120
F	+	0.3	-	2,560	1,280	20,480	20,480
G	+	0.3	-	-	-	-	-
H	+	0.3	-	-	-	-	-
I	+	3.0	-	-	-	10,240	10,240
J	+	3.0	-	-	-	40	5,120
K	+	3.0	-	-	-	DEAD	
L	+	3.0	-	-	-	-	-